Toxic Stress and Quality of Life in Early School-aged Ugandan Children with and without Perinatal Human immunodeficiency virus Infection

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Running Head: HIV, Stress and Wellbeing

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/cad.20355.

Abstract

Caregiver's and child's self-reported quality of life (QOL) was defined using standardized questionnaires in a sample (N=277) of 6-10 years old HIV-infected, HIV-exposed uninfected, and HIV-unexposed uninfected children from Uganda. Psychosocial stress (acute stress and cumulative lifetime adversity) and physiologic stress (dysregulations across 13 biomarkers), perinatal HIV status, and their interaction were related to child QOL via general linear models. Lower child- and caregiver-reported psychosocial stress were dose-dependently associated with higher QOL (acute stress: mean difference coefficient (b)= 8.1-14.8, effect size (ES) = 0.46 to 0.83). Lower allostasis was dose-dependently associated with higher QOL (b= 6.1-9.7, ES = 0.34 to 0.54). Given low caregiver acute stress, QOL for HIV-infected was similar to HIV-uninfected children; however, given high caregiver acute stress, a QOL disadvantage (b= -7.8, 95%CI: -12.8,-2.8; ES = -0.73) was evident for HIV-infected vs. uninfected children. Testing of caregiver stress reduction interventions is warranted to increase wellbeing in dependent children.

Keywords: Quality of life; HIV-exposed uninfected; Perinatal HIV-status; Functional Survival; Toxic stress; Pediatric HIV Infection; Psychosocial stress

BACKGROUND

Chronic human immunodeficiency virus (HIV) infection affects around 37 million individuals worldwide with 1.8 million new HIV infections in 2016 (UNAIDS). The morbidity and mortality profile for people living with HIV/AIDS (PLWHA) has improved due to highly active antiretroviral therapy (HAART). PLWHA now have improved life expectancy, quality of life (QOL) and slower progression to AIDS (T. C. Quinn, 2008). Furthermore, mother-to-child-transmission of HIV rate has declined to 1-2% (T. C. Quinn, 2008) from 25% in Europe/United States (Brocklehurst & Volmink, 2002) and 40% in low and middle income countries(UNAIDS, 2011) without treatment. Progress with survival and clinical management of HIV-infected individuals is undeniable but it is unclear whether infected persons survive and thrive with sufficient QOL, a multidimensional construct of wellbeing encompassing physical, psychological/emotional, social, environmental and spiritual domains. Research in mostly community dwelling older adults has shown that QOL is an independent predictor of mortality and functional survival. (Y. Lee, 2000) The impact of HIV infection on various dimensions of QOL remains an important area of study (Basavaraj, Navya, & Rashmi, 2010) especially in the current post-HAART era. However, specific information on this subject is limited for perinatally HIV infected or exposed children particularly during school-age and adolescent years of life.

Globally, HIV-related stigma and discrimination towards PLWHA have remained stable over time with a myriad adverse effects on their health outcomes (Arrey, Bilsen, Lacor, & Deschepper, 2017; Chambers et al., 2015; Li, Liang, Lin, & Wu, 2015; S. Rueda et al., 2016; Shacham, Rosenburg, Onen, Donovan, & Overton, 2015). These HIV-specific adverse experiences and routine life adversities compound the amount of psychosocial stress experienced by PLWHA with expected impact on their overall health (Au et al., 2004; Feng et al., 2015; Kingori, Haile, & Ngatia, 2015). Persistent stressful experiences like physical or emotional abuse, neglect, exposure to violence,

economic hardships or affliction with stigmatized conditions such as mental illness or HIV-infection may overwhelm the coping ability of the individual yielding toxic stress. In general pediatric population, toxic stress has been associated with developmental disadvantages including impaired neurocognitive development, sleep dysregulation, susceptibility to infection, and childhood obesity (Oh et al., 2018).

Two-thirds of all PLWHA including 85% of HIV-infected children reside in sub-Saharan Africa (SSA). (WHO, 2015) Among children and adolescents in Africa, AIDS-related illness remains the leading cause of death (Kisesa & Chamla, 2016) and thus the need for specific investigation of HIV-related QOL differences in the region. Investigations of both HIV and toxic stress as determinants of QOL outcomes among African PLWHA are few. A population-based investigation among adult African PLWHA noted HIV-associated QOL deficits relative to HIV-negative controls with/without HAART (Thomas et al., 2017). A meta-analysis (S. Rueda et al., 2016) of five studies (Abboud, Noureddine, Huijer, DeJong, & Mokhbat, 2010; Newman, Edmonds, Kitetele, Lusiama, & Behets, 2012; Slater et al., 2013; Tam et al., 2012; Vyavaharkar, Moneyham, Murdaugh, & Tavakoli, 2012) in adult PLWHA noted the association between HIV-related stigma and lower QOL, (S. Rueda et al., 2016) but only three studies implemented adjustments for potential confounders, (Abboud et al., 2010; Slater et al., 2013; Tam et al., 2012) and only one study was conducted among African PLWHA (Newman et al., 2012). Hence, rigorous investigations of stress-related differences in QOL among PLWHA from resource constrained settings are lacking, particularly among children.

A large cross-sectional study of American children recruited as part of the pediatric AIDS Clinical trial group reported worse psychological functioning for HIV exposed uninfected (HEU) compared to perinatally HIV infected(PHIV) even though physical functioning was similar (G. M. Lee, Gortmaker, McIntosh, Hughes, Oleske, et al., 2006). Among PHIV and PHEU children from India, PHIV had QOL disadvantage relative to HEU in all domains of QOL with the exception of

discrimination (Das et al., 2017). Another study among school-aged children in Uganda confirmed deficits in QOL for PHIV relative to HEU and HIV-unexposed uninfected (HUU) community controls, but did not consider toxic stress risk factor (Nkwata et al., 2017). The contribution of toxic stress to QOL differences – including the possible variations in this relationship by perinatal HIV status has not been specifically studied. Hence in this study we investigated perinatal HIV and toxic stress as independent and joint determinants of QOL in a sample of 277 HIV affected/unaffected school-aged Ugandan children. We hypothesized that QOL would be lower among children with higher levels of toxic stress. We further hypothesize that HIV-related differences in QOL may vary according to levels of toxic stress.

METHODS

Study design and participants

School aged (6 – 10 years old) children with and without perinatal HIV infection/exposure and their adult caregivers were recruited between March 15, 2018 and September 15, 2018. Participants were enrolled from the Kawempe Division of Kampala, which has Uganda's highest regional HIV prevalence (11%), compared to national prevalence of 7.3%. (Giordani et al., 2015) To ensure objective verification of HIV status and peripartum birth history for children and their birth mothers, only children born in a hospital/healthcare setting were included. Hence, we excluded children born in non-clinic settings and children of caregivers without official birth records and/or missing antenatal register/delivery medical records. Current HIV-status of HEU and HUU children was ascertained using HIV-rapid diagnostic test at enrolment.

HIV-infected children were recruited from children actively enrolled in HIV-care at Kawaala health center (KHC) in Kampala, Uganda. KHC delivers the full range of antenatal care services, out-patient consultation, and the entire range of HIV/AIDS treatment and preventive services. HIV-

exposed uninfected children were identified through antiretroviral therapy cards of HIV-infected adult women currently in care at KHC. In addition, the Early Infant Diagnosis registers was used to identify age-eligible children born to HIV-infected women that remained HIV-free until discharge from the early diagnosis program at KHC. Lastly, research assistants enrolled age-eligible HIV-negative children (HUU and HEU) from the Out Patient Department of KHC and from the social networks of HIV-affected children.

Ethical approval

The study protocol was approved by the research ethics review committees of Michigan State University (IRB Protocol#:16-828), Makerere University College of Health Sciences, School of Medicine (Protocol REC REF#: 2017-017) and the Uganda National Council for Science and Technology (Protocol #: SS4378). All caregivers gave written informed consent and children provided assent for study participation.

Measures

Outcome: Child's QOL

Each Child's QOL was assessed from both child's (i.e. self-report) and respective caregiver's (i.e. proxy report) perspectives using appropriate versions of Pediatric Quality of Life Inventory (PedsQL^{TM} 4.0) questionnaire (Varni, Seid, & Kurtin, 2001; Varni, Seid, & Rode, 1999). Four QOL domains – the absence of fatigue or presence of vitality/vigor based on the multidimensional fatigue scale (MDFS/MDV), perception of general well-being (GWB) in past 30 days and present functioning impairment/limitation (PFI), and combined quality of life inventory (QOL) were defined for each

child (Varni et al., 2001; Varni et al., 1999). Child self-report of GWB and PFI was only possible in children ≥8 years old. QOL scores were computed in each domain on the scale from 0 (lowest QOL) to 100 (highest QOL). The QOL included four sub-scales – physical, emotional, school and social function, and MDFS included three subscales: general, sleep, and cognitive fatigue. Each subscale score is a composite of six questions. The initial translation, adaptation and validation of QOL tool for this setting have been described elsewhere (Zalwango et al., 2016). The internal consistency of questionnaire items in the QOL, MDV, GWB and PFI scales demonstrated acceptable reliability in each of the proxy or self-reported QOL domains (Cronbach's-a= 0.7 to 0.91). Similarly, all corresponding QOL and MDV subscales confirmed each QOL subscale had acceptable reliability regardless of respondent (Cronbach's-a: 0.65 to 0.87).

Primary Exposures

Child's Perinatal HIV Status: HIV infection was restricted to perinatal mother-to-child transmission that had occurred by the end of breast-feeding and was confirmed objectively using DNA PCR. In addition to perinatally HIV infected (PHIV) children of HIV-positive women, perinatally HIV-exposed uninfected (HEU) children of HIV-positive women and perinatally HIV-unexposed uninfected (HUU) children of HIV-negative women were also defined.

Psychosocial Stress: We measured acute, recent and lifetime psychosocial stress in caregivers and children using standardized questionnaires adapted and translated for the study setting.

1. **Acute Stress** was the sum of occurrence for ten stressful unexpected experiences/and the extent to which a person has felt in control of these situations over the past month was assessed using the perceived stress scale (Glover, Garcia-Aracena, Lester, Rice, & Rothram-Borus, 2010).

2. **Recent Stress was** defined as the sum of occurrence of 19 adverse events in the most recent 5-year period for the caregiver only using the recent life events questionnaire. (Brugha, Bebbington, Tennant, & Hurry, 1985).

3. **Major Adverse Lifetime Experiences / Lifetime Adversity** was defined as the sum of 17 adverse experiences over the lifetime for children, consistent with the adverse childhood experiences questionnaire. (M. Quinn et al., 2018) Lifetime adversity in adults was defined using the stressful life event questionnaire. (Roohafza et al., 2011)

Since each domain of stress was assessed using a checklist, the internal consistency reliability was not applicable. For each summed psychosocial stress measure, five categories were using the approximate quintile of each variable in the absence of risk threshold determined based on population norms to test hypothesis that lower levels of stress is associated with higher quality of life without the stringent assumption of linearity sample quintiles. Lower levels of stress (quintiles one, two, three and four) were compared to highest (fifth) stress quintile in all analyses.

Physiological Stress: Children's physiological stress was measured using 13 biomarkers indexed according to the allostatic load model (McEwen, 2006; McEwen & Seeman, 1999) to quantify stress related dysregulation across growth, immune, metabolic, cardiovascular and neuroendocrine physiological systems (Glover et al., 2010). We specifically defined physiological stress as sum of abnormal levels present for 13 biomarkers needed for maintenance of stability in the immune (platelets, neutrophils), metabolic (HDL, LDL, Albumin, Creatinine), neuroendocrine (Cortisol, Dopamine, Epinephrine & Norepinephrine) and cardiovascular (Systolic BP, Diastolic BP) systems and growth (height-for-age). Four categories of allostatic load- each defined by approximate quartile of the continuous variable, were defined. The lower quartiles (one to three) were compared to the highest (i.e. fourth) quartile in all analyses.

Other Measures

Detailed sociodemographic, medical history, physical examination and laboratory evaluations were performed on all child-caregiver pairs. Perceived social standing was measured as caregiver's subjective self-ranking with respect to prestige, social status and privilege in their community at this point in their life using the MacArthur Scale (Cundiff, Smith, Uchino, & Berg, 2013). Medical records, i.e., antenatal registers and notes, birth passports and antiretroviral therapy cards, were reviewed to ascertain child's birth weight and APGAR score at birth. These records were also used to verify biological mother's HIV-status/antiretroviral therapy status in pregnancy and establish the child's HIV status at birth. Physical examination at enrolment were performed by clinicians to establish current health status.

Laboratory investigations included: rapid diagnostic test (RDT) for malaria followed by blood smear if RDT was positive; complete blood counts to establish hematologic indices; assessments for free urinary metabolites including cortisol, catecholamines and creatinine; lipid profile tests to establish serum cholesterol/triglyceride levels; blood biochemistry to quantify serum albumen, c-reactive protein; and fasting glucose levels and stool tests for helminth infections, protozoa and other intestinal parasites. Measures of cortisol and urinary metabolites were assessed via mass spectrometry using the first Saturday morning urine following enrolment date in order to limit variations in urine metabolites by time of day and weekly activity patterns.

Statistical analyses

Internal consistency reliability for scales was assessed using Cronbach's alpha coefficients (Cronbach. L, 1951). Means, standard deviations (SD), frequencies, and percentages were estimated

by perinatal HIV infection status. Comparisons of HIV exposure groups were performed using *t* tests for continuous variables and X^2 tests for categorical variables**.**

Following univariate and bivariate analyses, multivariable linear regression analyses were implemented (Tibshirani, 2011). Confounders – such as child's age (as continuous covariate), sex (female vs. male), relationship with caregiver (biological vs. non-biological parent), caregivers' age (as continuous covariate), sex (female vs. male) and socio-economic status (presence vs. absence of own income), were adjusted for in light of subject matter knowledge. Regression models estimated HIV- and stress-related percent differences (b) in QOL scores and 95% confidence intervals (CI). Because multiple children from the same households were enrolled in some cases, clustered of children within households was accounted for by specifying the random effect of the household.

The potential for interaction between perinatal HIV infection and toxic stress was evaluated by introducing an HIV*stress interaction in multivariable model including respective individual effects. Because of the exploratory nature of the analysis with the interaction terms, p-values< 0.10 were used to indicate potential effect modifications. (Marshall, 2007) All analyses were performed with SAS version 9.3 (SAS Institute, Inc. Cary, NC) and *p*-values of less than 0.05 were used to indicate statistical significance. Effect size (ES) estimates were calculated as b/√ (mean square error) of applicable multivariable models for each comparison as a complimentary non p-value based measure of association to gauge the clinical relevance of estimated HIV- and toxic stress- related differences in QOL. Per Cohen criteria and specific meta-analysis designed to establish the minimally important difference individuals are able to discriminate for across range of tools used to measure QOL,(Cella et al., 2002; Norman, Sloan, & Wyrwich, 2003; Rothrock et al., 2010) estimated ES values are interpreted as follows: very small: |ES|<0.20, small:0.20<= |ES| <0.33, moderate:0.33<= |ES| <0.50, large: 0.50<= |ES| <0.80 and very large: |ES|>=0.80. With the available sample size, effect sizes of 0.42 or greater were detectable as statistically significant with power of 0.80 or greater

in two-tailed tests at .05 level of significance for pairwise differences in QOL among HIV groups. In the analyses using stress quintiles, the detectable effect size was 0.51.

RESULTS

Description of Salient Sociodemographic Factors, Toxic Stress and QOL in Study Base

A total of 277 children from 224 unique households were analyzed. Caregivers were between 19 and 67 years old, mostly female, and majority had elementary education or less (Table 1). By design two-thirds of caregivers lived with HIV themselves (n=147 or 62.6%). On average, caregiver and child self-reported MDFS scores were similar by perinatal HIV status as were scores in present functioning, general wellbeing, and rating of general health. Few exceptions included the sleep rest fatigue subscale of caregiver-reported MDFS and child cumulative lifetime adversity.

With respect to current child health indicators, mean levels of hemoglobin, HPA Axis hormones and white blood cell indices were similar by perinatal HIV groups but PHIV had large height-for-age growth deficit compared to HEU or HUU. Similarly, the levels of inflammatory markers were higher and prevalent metabolic/lipid profile dysregulation and anemia of any type (particularly macrocytic anemia) was greater for PHIV compared to other groups (Table S1). Average scores in several child-reported QOL outcomes decreased markedly with increasing physiologic stress but proxy reported QOL measures were similar across physiologic stress quartiles. (Table 2)

Child Physiologic and Psychosocial Stress in Relationship to Child-reported Wellbeing

Low allostasis (AL ≤1 vs. ≥3) was associated with higher child-reported QOL and MDV (all ES≥0.5) but not with child-reported GWB or PFI (Table 3). Low child acute stress (quintiles ≤4 vs 5)

was associated with 0.46 to 0.83 SDs higher QOL (b=8.1–14.8, all P<0.02), and with 0.29 to 0.95 SDs higher MDV (quintiles ≤2 vs 5, b=14.4–14.6, P<0.01). Likewise, all lower vs. highest quintiles of child-reported lifetime stress were consistently and dose-dependently associated with higher child-reported QOL (quintiles ≤3 vs. 5: b=11.4 to 18.0, ES: 0.64 to 1.01) and enhanced vitality/vigor (quintiles ≤3 vs. 5: b=8.0 to 16.8, ES: 0.52 to 1.09). Among 8 – 10 years old children, low lifetime stress was associated with enhanced GWB (quintile 2 vs. 5: b=10.7, 95%CI: 1.3 to 23.2) and at least 0.6 SDs lower PFI (quintiles ≤2 vs 5, b=-11.1 to -13.1, P<.04) (Table 3).

High Caregiver Psychosocial Stress is Inversely Associated with Dependent Children's QOL

Caregiver acute stress measures were strongly and inversely associated with caregiver-reported child QOL measures. Specifically, caregiver-reported QOL was 0.7 standard deviations (SD) higher QOL (b = 7.5), MDV score was 0.52 SDs higher (b = 6.4) for children whose caregivers reported the least vs. highest acute stress. Similarly, the three lower vs. highest quintile of caregiver recent life stress was dose dependently associated with 0.66 to 0.76 SDs higher QOL (b = 7.0 to 8.1), 0.63 to 1.08 SDs higher MDV (b = 8.5 to14.4), and 0.63 to 0.81 SDs lower PFI (b = -8.1 to -7.3), in dependent children. Similarly, QOL was on average 8.5 points higher (95% CI: 5 – 15), MDV was 12.2 higher (95CI: 7 to 20), PFI was 9.9 lower (95% CI: -15 to -6) and GWB was 7.3 higher (95% CI: 0.4 to 12.5) for children whose caregivers reported the lowest vs. highest lifetime adversity. (Table 4)

Perinatal HIV status and Relationship to Child Wellbeing Depends on Acute Caregiver Stress

In the multivariable analysis, perinatal HIV status and caregivers' HIV-status weren't independently associated with QOL as main effects. However, the relationship between Perinatal HIV status and three caregiver-reported QOL measures – QOL (Caregiver stress*Perinatal HIV, P=0.005), MDV (Caregiver stress*Perinatal HIV, P=0.004) and PFI scales (Caregiver stress*Perinatal HIV, P=0.100), varied according to caregiver acute stress level. On one hand, among children whose caregivers reported low acute stress, no perinatal HIV-status related differences observed in QOL and

its associated subscales (Figure 1). However, dependent PHIV vs. HUU children of caregivers reporting high acute stress were at QOL disadvantage (ES = -0.73, b= -7.8, 95%CI: -12.8 to -2.8) with strongest deficits evident in the physical (ES=-0.71, b= -10.2, 95%CI: -16.8 to -3.6) and school (ES=-0.44, b= -7.4, 95% CI: -14.3 to -0.5) function subscales. (Figure 1)

The protective role of low caregiver stress for child wellbeing was also evident for MDV and two of its subscales- sleep/rest and cognitive vitality. An advantage in general vitality subscale was evidence for PHIV vs. HUU in low caregiver acute stress environments (ES=0.50, b=8.9, 95% CI: 1.6 to 16.3). This protective association was absent in high caregiver acute stress environments, where general vitality score (ES=-0.71, b= -9.9, 95%CI: -17.3 to -2.6), sleep rest vitality score (ES=-0.44, b = -9.7, 95%CI: -16.3 to -3.0) and MDV (ES=-0.73, b= -8.0, 95% CI: -13.7 to -2.3) were all lower , whereas PFI was higher (ES=0.44, b= 5.0, 95%CI: 0.1 to 9.9) for PHIV vs. HUU. (Figure 2)

DISCUSSION

In this cross-sectional analysis, psychosocial stress, as measured by perceived stress and recent life events questionnaire, was not substantially elevated in HIV-affected relative to HIV-unaffected households. The number of caregiver reported lifetime adversities in this setting was highest among HEU while child reported lifetime adversity level was highest among HUU households and aligns with previously described higher levels of negative lifetime events among American HEU children (G. M. Lee, Gortmaker, McIntosh, Hughes, & Oleske, 2006). The average number of dysregulated biomarkers of physiologic stress was highest in PHIV although difference across perinatal HIV-groups was not statistically significant. However, caregiver reported acute stress levels observed in this sample was high relative to average values in normative sample of adults of similar age from the United States (Cohen & Janicki-Deverts, 2012). These observations combined with noted low levels of education and low perceived social standing that was similar across HIV groups

to suggest that psychosocial stress and adversity of the life-course in this setting is high regardless of HIV-status.

The inverse association between child psychosocial stress and child-reported QOL is reinforced by: a) observation of corresponding inverse association between objectively measured physiologic stress and child reported QOL and b) negative associations between dependent children's QOL and their caregivers' levels of acute, recent and lifetime stress. These findings are in line with the prior reports establishing the importance of caregivers' socioemotional state for wellbeing of their dependent children (Webster et al., 2019). Of importance, association of toxic stress with child wellbeing in this sample was dose dependent and clinically significant with effect sizes often in excess of 0.5 standard deviations regardless of respondent (Norman et al., 2003). Of note, per child reported toxic stress measures, the association of stress with child-wellbeing did not vary by HIV-status suggesting that interventions to reduce or manage high psychosocial and physiologic stress in this population could be broadly beneficial to caregivers and dependent children regardless of HIV exposure.

We found no evidence that caregiver's HIV-positive status was associated with worse wellbeing in their dependent children. This observation is reassuring in the era of universal HAART and confirms previous observation of no caregiver HIV-status related difference in psychosocial adjustment of Ugandan children. (Webster et al., 2019) As would be expected, the vast majority of caregivers in this study were female (mothers). We did not have sufficient number of primary male caregivers to robustly evaluate similarity in wellbeing by male caregiver status. Unlike studies in the pre-HAART era when HIV-positive status related differences in wellbeing of dependent children was driven by low CD4 cell count, advanced HIV/AIDS disease stage, lack of HAART/treatment adherence, severity of illness and severe HAART related toxicities, (Charles et al., 2012; Jaquet et al., 2013; Sergio Rueda et al., 2016; Stangl, Wamai, Mermin, Awor, & Bunnell, 2007) having a healthier

HIV-positive mother allows children to derive the same developmental advantage enjoyed by their HIV-unaffected peers.

As previously reported among Ugandan school-aged children, we found QOL measures to be largely similar for HEU vs. HUU (Nkwata et al., 2017). We demonstrate that PHIV-status itself was associated with poor child-wellbeing only in caregiving environments characterized by high levels of caregiver stress. This observation confirms the benefit of effective HIV care for PHIV but also highlights opportunities for adjunct interventions to sustain the benefit of excellent HIV care by enhancing the capacity of HIV-affected households to cope with psychosocial adversity including caregiver depression (Familiar et al., 2016) related to their HIV-affected status. On the one hand, PHIV were similar to uninfected children in most QOL measures, with possible higher general vitality than uninfected peers, but only in low caregiver stress environments. Further, PHIV are vulnerable to a range of QOL deficits in high caregiver stress environments. Hence, psychosocial interventions to mitigate toxic stress will support optimal development of all children with higher benefit for PHIV among whom psychosocial adversity down modulates QOL despite optimal HIV-care.

This study is subject to the limitations of a cross-sectional design which place significant constraints on causal inference permitting only associations between toxic stress and respective QOL measures on the basis of this study. Further, the relationship between stress and QOL though internally valid, may not be maximally externally generalizable to a different sample because thresholds specific to this sample were used define levels of toxic stress in the absence of locally relevant validated cut-offs for respective stress scales. Future longitudinal studies including repeated assessments of toxic stress and QOL measures will be important to determine temporal sequence and potential toxic stress related differences in QOL trajectory in this sample. These limitations notwithstanding, the assessment of QOL using multidimensional tools previously validated in this setting with good reliability in the current sample are important strengths that highlight the rigor and

appropriateness of QOL assessments in this study. Additional strengths lie in the measurement of both toxic psychological and physiological stress in dependent children which allows for assessment of coherence in the association of various measures of stress with QOL. Further strengths that should increase confidence in the findings reported herein, include implementation of a robust analytic strategy with control for important child, caregiver and contextual confounders and the estimation of effect sizes to evaluate the clinical importance of observed risks as a complement to mean differences as a measure of association.

CONCLUSION

In summary, modifiable physiologic and toxic psychosocial stress are associated with quality of life in vulnerable African children. All children thrive in low stress environments with PHIV exhibiting vulnerability in several QOL domains within high stress environments. Specific biopsychosocial interventions that enhance the capacity of individuals to cope with psychosocial stress and/or reduce the intensity/frequency of toxic stress are needed and if implemented will benefit all children in household units regardless of HIV status.

Table 1: Descriptive Summary of Measures of Key Variables and measures of Child wellbeing over the past month according to perinatal HIV Status

	Overall N=277	**PHIV N=92**	**HEU N=93**	**HUU N=92**	**p for PHIV, HEU, HUU comparison**
Child Socio-demographic& Stress Factors					
Child Age (Years, mean, SD)	7.7 (1.5)	7.7 (1.4)	7.5 (1.4)	7.9 (1.5)	0.070
Female Sex (n, %)	154 (50)	48 (46)	55 (55)	51 (48)	0.463
Growth/Anthropometric Indices					
Body mass index z-score	-0.62 (1.05)	-0.53 (1.02)	-0.69 (1.02)	-0.75 (1.14)	0.369
Height for age z-score	-0.58 (1.05)	-0.89 (0.95)	-0.41 (1.17)	-0.37 (1.00)	0.006
Child-reported Psychosocial & Physiologic Stress Measures	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
# Adverse lifetime experiences	3.8 (4.1)	3.9 (4.0)	3.0 (3.6)	4.5 (4.5)	0.053
Acute Stress score	13.2 (5.4)	13.0 (5.8)	13.3 (5.0)	13.4 (5.4)	0.874
Physiologic stress/Allostasis Score	1.8 (1.33)	2.0 (1.4)	1.7 (1.35)	1.6 (1.3)	0.082
Caregiver Sociodemographic Factors*					
Age (in years)	34.1 (8.1)	**34.2 (8.9)**	**35.7 (8.0)**	**33.7 (8.4)**	0.234
	N (%)	N (%)	N (%)	N (%)	
Female	254 (92)	81 (90)	87 (94)	86 (92)	0.682
% Ever HIV+	170 (61)	69 (77)	88 (95)	13 (14)	<0.001
Very good/excellent Self-rated Health	187 (70)	62 (71)	64 (72)	61 (66)	0.594
% married/living with partner	124 (45)	38 (42)	32 (35)	54 (58)	0.008
Ever Alcohol use	110 (40)	36 (40)	39 (43)	35 (37)	0.737
Has own income	201 (74)	64 (73)	67 (74)	70 (75)	0.965
Formal Education Attained None/ < Elementary Elementary completed Some/Completed O' levels Some A' levels or more	105 (38) 55 (20) 59 (32) 26 (10)	34 (38) 15 (17) 33 (37) 8 (9)	45 (50) 20 (22) 24 (26) 2 (2)	26 (28) 20 (21) 32 (34) 16 (17)	0.004
Caregiver Psychosocial Stress	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Acute Stress Score	21.9 (5.5)	21.1 (5.7)	22.8 (4.9)	21.6 (5.9)	0.098
Recent Life stress (within 5 years)	12.6 (6.5)	12.0 (6.3)	12.7 (6.4)	13.3 (5.0)	0.391
# Adverse Lifetime Experiences	3.0 (2.8)	2.5 (2.5)	3.8 (3.3)	2.5 (2.4)	0.001
Perceived Social Standing Score on McArthur Scale	3.3 (1.6)	3.4 (1.5)	3.0 (1.6)	3.3 (1.6)	0.244
Caregiver-reported Child QOL*	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
1. Combined QOL Scale	84.6 (11.8)	83.9 (12.4)	85.6 (11.1)	84.5 (11.8)	0.475
Physical Functioning	89.0 (15.1)	87.6 (17.3)	91.3 (13.4)	88.9 (13.9)	0.249
Emotional Functioning	78.6 (16.9)	78.0 (17.6)	79.6(17.1)	77.6 (15.9)	0.697
Social Functioning	91.5 (13.0)	91.7 (13.2)	92.7 (11.0)	90.9 (14.7)	0.543
School Functioning	79.1 (18.7)	77.6 (18.0)	78.6 (19.5)	77.9(18.8)	0.937
2. Multidimensional Vitality/Vigor Scale	83.6 (14.4)	81.8 (14.4)	84.9 (13.2)	82.3 (15.5)	0.312
General vigor	81.2 (19.2)	80.1 (18.4)	82.8(18.1)	78.6 (20.8)	0.339
Sleep rest vigor	91.7 (14.7)	89.1 (16.6)	94.3 (11.7)	91.3 (14.9)	0.083

Cognitive vigor	77.7 (23.4)	76.3 (23.3)	77.9 (22.9)	77.0 (24.0)	0.900
3. Present Functioning Impairment Scale	5.5 (11.4)	6.4 (10.7)	3.3 (9.5)	7.0 (13.6)	0.038
4. General Wellbeing Scale	73.2 (14.5)	72.8 (16.8)	74.4(14.0)	72.3 (15.4)	0.569
Child Self-Report of Own QOL					
1. Combined QOL Scale	79.4 (15.8)	78.0 (14.3)	82.3 (15.2)	78.1(17.6)	0.108
Physical Functioning	83.2 (16.6)	81.8(16.8)	84.8(15.2)	81.8 (16.7)	0.447
Emotional Functioning	78.7 (19.5)	77.3 (19.1)	82.0 (17.9)	77.4 (21.2)	0.174
Social Functioning	79.2(21.3)	77.8 (19.7)	82.8 (21.1)	76.7 (22.7)	0.115
School Functioning	76.2 (20.9)	73.4 (21.1)	79.4 (19.7)	76.1 (21.5)	0.156
2. Multidimensional Vitality/Vigor Scale	75.8 (18.7)	74.1 (17.6)	79.0 (16.7)	74.3 (21.2)	0.145
General vigor	78.5 (21.8)	76.5 (21.8)	83.4 (19.0)	75.3 (23.5)	0.028
Sleep rest vigor	80.9 (22.2)	79.4 (19.8)	84.8(21.4)	78.4 (24.7)	0.116
Cognitive vigor	68.1 (26.5)	66.6 (27.2)	68.7 (25.6)	69.4 (26.6)	0.752
3. Present Functioning Impairment Scale **	8.8 (16.2)	9.5 (16.2)	6.5 (12.4)	12.0 (19.1)	0.290
4. General Wellbeing** (n=147)	74.5 (16.4)	72.1 (16.2)	78.4 (15.1)	74.5 (17.3)	0.182

**For descriptive purposes, number (%) and mean (SD) of children under care in context of respective caregiver factors are presented. Hypothesis testing is not adjusted for potential clustering of children within caregivers.*

***These questionnaires are only administered in children eight years and older. PHIV= perinatally HIV infected, HEU = Perinatally HIV exposed Uninfected, HUU = HIV unexposed Uninfected (Control)*

Table 2: Child's Reported QOL over the Past Month by Quartiles of Child's Physiologic Stress					
	Quartile 1 (n=53)	Quartile 2 (n=79)	Quartile 3 (n=70)	Quartile 4** (n=76)	**p for comparison across quartiles**
Caregiver Report of Dependent Children's QOL	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
1. Combined QOL Scale	86.3(11.7)	83.0 (11.1)	84.7 (11.7)	84.4 (11.6)	0.454
Physical Functioning	91.8 (13.3)	87.3 (15.5)	89.8 (16.6)	88.5 (13.1)	0.397
Emotional Functioning	79.8 (17.6)	76.7 (15.5)	81.0 (16.6)	77.0 (17.0)	0.306
Social Functioning	93.7 (13.2)	90.3 (13.1)	90.4 (12.6)	92.5 (12.3)	0.289
School Functioning	79.9 (18.0)	77.6 (17.9)	76.9 (17.7)	78.8 (18.5)	0.853
2. Multidimensional Vitality/Vigor Scale	83.8 (14.4)	82.0 (14.0)	83.2 (13.4)	83.6 (15.2)	0.891
General vigor	83.7(18.4)	79.2 (18.6)	80.7 (19.0)	80.1 (19.2)	0.582
Sleep rest vigor	90.9 (16.2)	89.6 (15.9)	93.0 (10.6)	92.4 (16.3)	0.510
Cognitive vigor	76.8 (24.6)	77.1 (22.2)	75.9 (23.9)	78.3 (21.4)	0.938
3. Present Functioning Impairment Scale	3.4 (9.6)	7.1 (12.7)	5.8 (8.4)	5.1 (14.0)	0.301
4. General Wellbeing Scale	74.1(14.2)	73.1 (13.0)	73.3 (19.3)	73.0 (13.9)	0.947
Child Self-Report of Own Quality of Life					
1. Combined QOL Scale	81.4 (15.4)	82.8 (11.7)	80.4 (16.1)	73.8 (18.3)	0.003
Physical Functioning	86.7(15.1)	86.1(13.2)	82.5 (19.1)	78.1 (19.1)	0.007
Emotional Functioning	79.0 (19.5)	82.1 (17.8)	81.2 (17.7)	73.5 (21.7)	0.031
Social Functioning	81.8 (21.9)	81.1 (21.0)	81.3 (19.5)	73.1 (24.1)	0.044
School Functioning	78.5 (19.5)	81.5 (17.5)	76.1 (21.0)	69.5 (23.8)	0.004
2. Multidimensional Vitality/Vigor Scale	76.2(17.6)	80.2 (16.0)	76.7 (20.2)	70.1 (21.3)	0.010
General vigor	79.2 (21.8)	81.4 (20.9)	78.9 (23.5)	74.4 (24.2)	0.266
Sleep rest vigor	81.5 (21.8)	84.7 (17.7)	83.5 (23.5)	74.0 (24.9)	0.014
Cognitive vigor	67.9 (25.2)	74.8 (24.6)	67.8 (29.2)	62.0 (26.7)	0.026
Present Functioning Impairment Scale* (n=148)	10.8 (18.8)	6.4 (16.4)	11.8 (21.6)	8.8 (11.3)	0.590
General Wellbeing Scale* (n=147)	73.2 (17.8)	77.1 (15.8)	69.7 (16.1)	77.9 (18.8)	0.142

TABLE 3: Allostatic Load and Child-Reported Psychosocial Stress as Determinants of Child self-reported Quality of Life in Ugandan Children 6 – 10 years old*

	Combined QOL Score	**Multi-dimensional Vitality/Vigor Scale**	**General Wellbeing Scale**	**Present Functioning Impairment Scale**
Perinatal HIV Status	**b (95% CI), ES**	**b (95% CI), ES**	**b (95% CI), ES**	**b (95% CI), ES**
PHIV vs. HUU	3.4 (-1.4, 8.1), 0.19	4.1 (-1.0, 9.2), 0.27	-2.4 (-8.5, 3.8), -0.15	-4.6 (-11.7, 2.5), -0.29
HEU vs. HUU	0.04 (-4.8, 4.9), 0.02	1.2 (-3.7, 6.1), 0.08	5.8 (-0.4, 12.1), 0.36	-5.4 (-11.8, 1.0), -0.34
Allostatic Load				
Q1 (least)	**8.4 (2.2, 14.6), 0.47**	**7.3 (0.5, 14.2), 0.47**	-5.8 (-13.2, 1.6), -0.36	3.5 (-4.8, 11.8), 0.21
Q2	**9.7 (3.4, 16.1), 0.54**	**9.7 (3.8, 15.6), 0.62**	0.8 (-6.5, 8.1), 0.04	-2.3 (-8.2, 3.6), -0.14
Q3	6.1 (-0.7, 13.0), 0.34	**7.4 (1.2, 13.6), 0.48**	-6.4 (-13.8, 1.0), -0.39	2.6 (-5.3, 10.5), 0.16
Q4 (most)	Ref	Ref	Ref	Ref
Child Acute Stress				
Q1(Least Stressed)	**14.8 (8.8, 20.8), 0.83**	**14.4 (8.2, 20.7), 0.94**	**6.2 (-2.5, 15.0), 0.38**	**-13.1 (-19.2, -7.0), -0.82**
Q2 v. 5	**14.0 (7.2, 20.8), 0.79**	**14.6 (8.2, 21.1), 0.95**	**7.0 (-2.4, 16.5), 0.43**	**-11.1 (-18.2, -4.0), -0.69**
Q3 v. 5	**9.0 (2.0, 16.0), 0.51**	4.5 (-2.1,	2.9 (-5.3, 11.1),	-3.9 (-12.5, 4.7), -0.24

		12.4), 0.29	0.18	
Q4 v. 5	**8.1 (1.3, 14.9), 0.46**	4.5 (-3.3, 12.4), 0.29	7.6 (-0.6, 15.7), 0.47	-3.9 (-12.9. 5.1), -0.24
Q5 (Most stressed)	Ref	Ref		Ref
Child Lifelong Stress				
Q1(Least Stressed)	**13.8 (7.6, 19.9), 0.78**	**13.2 (6.8, 19.6), 0.86**	8.8 (-0.8, 18.3), **0.54**	**-8.7 (-16.4, -1.0), -0.55**
Q2 v. 5	**18.0 (12.4, 23.7), 1.01**	**16.8 (10.5, 23.2), 1.09**	**11.0 (1.9, 20.1), 0.67**	**-13.8 (-21.7, -5.9), -0.87**
Q3 v. 5	**11.4 (5.0, 17.8), 0.64**	**8.0 (1.8, 14.1), 0.52**	5.6 (-2.0, 13.2), 0.34	**-9.5 (-16.8, -2.1), -0.60**
Q4 v. 5	6.1 (-0.7, 12.9), 0.34	3.0 (-4.0, 10.1), 0.19	4.4 (-2.7, 11.4), 0.27	-2.2 (-10.2, 5.9), -0.14
Q5 (Most stressed) v. 5	Ref	Ref	Ref	Ref

**These questionnaires are only asked of children eight years and older; **: Q1 = all biomarkers normal; Q2 = 1 biomarker dysregulated; Q3 = 2 biomarkers dysregulated, Q4 = 3, 4, 5 or 6 concurrent dysregulations. Regression models are adjusted for child age, sex, HIV status, social standing, caregiver age, LBW and 5 minutes post birth apgar score.*

*

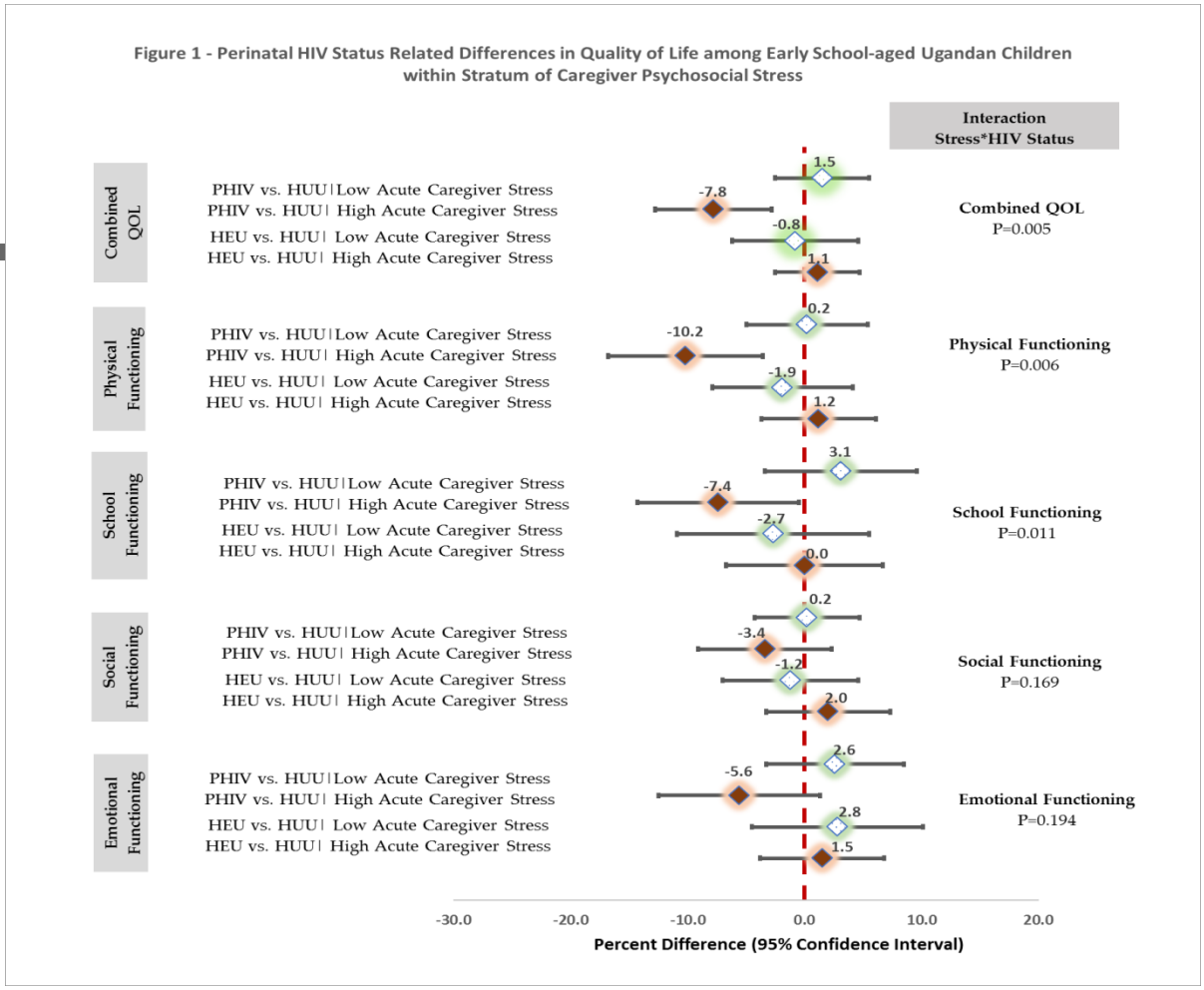
TABLE 4: **Caregiver Psychosocial Stress Related Differences in QOL for Ugandan School aged Children 6 – 10 years old****

	Combined QOL	**Multidimensional Vigor/Vitality Scale**	**Present Functioning Impairment**	**General Wellbeing Scale**
	b (95% CI), ES	**b** (95% CI), ES	**b** (95% CI), ES	**b** (95% CI), ES

Perinatal HIV Status				
HIV Exposed	0.7 (-2.4, 3.9), 0.07	2.6 (-1.6, 6.8), 0.20	-3.02 (-6.6, 0.55), -0.26	-0.64 (-4.7, 3.4), -0.05
HIV Infected	-3.02 (-6.3, 0.24), -0.28	-2.6 (-6.5, 1.3), -0.20	1.6 (-1.8, 5.0), 0.14	-0.06 (-4.7, 3.9), 0.00
HUU	Ref	Ref	Ref	Ref
Caregiver depressed vs. not depressed	**-5.3 (-8.2, -2.3), -0.50**	-4.3(-7.9, -0.74), -0.31	1.86 (0.4, 7.1), 0.16	-0.58 (-4.0, 2.8), -0.04
Age of Caregiver (yrs)				
18 – 28	**-4.9 (-8.7, -2.8), -0.46**	-3.6 (-8.1, 0.8), -0.27	-0.6 (-3.1, 4.7), -0.05	-4.0 (-7.4, 3.5), -0.29
29 – 33	**-4.4 (-7.5, -0.5), -0.41**	-3.0 (-7.7, 1.7), -0.23	-0.2(-4.6, 4.3), -0.02	0.15 (-4.6, 4.9), 0.01
34 – 38	**-6.2 (-9.1, -2.2), -0.58**	-3.1 (-7.5, 1.3), -0.23	3.3 (1.8, 9.1), 0.29	-1.04 (-5.8, 3.7), -0.07
39+	Ref	Ref	Ref	Ref
Caregiver Acute Stress				
Q1 (Least) vs Q5	**7.5 (2.8, 12.1), 0.70**	**6.9 (1.21, 12.0), 0.52**	-0.98 (-5.1, 4.5), -0.09	2.1 (-3.8, 7.9), 0.15
Q2 v. 5	3.3 (-1.9, 7.7), 0.31	1.4 (-2.9, 7.6), 0.10	**2.4 (-2.2, 6.9), 0.21**	-3.4 (-8.3, 1.4), -0.24
Q3 v. 5	3.9 (-0.8, 9.0), 0.36	**5.6 (1.4, 11.8), 0.42**	1.8 (-3.0, 6.7), 0.16	0.3 (-4.2, 4.8), 0.02
Q4 v. 5	4.5 (-0.37, 9.6), 0.42	**6.8 (0.7, 11.7), 0.51**	0.5 (-3.3, 6.9),0.04	-1.4 (-5.8, 3.0), -0.10
Q5 (Most)	Ref	Ref	Ref	Ref
Caregiver Recent Life Stress				
Q1 (Least) vs Q5	**8.1(1.12, 12.3), 0.76**	**14.4 (8.3, 20.5), 1.08**	**-9.3(-14.4, -4.1), -0.81**	5.2 (-6, 11.4), 0.37
Q2 v. 5	**7.7 (1.3, 11.2), 0.73**	**11.2 (4.8, 17.6), 0.84**	**-7.3 (-12.5, -2.1), -0.63**	1.9 (-4.2, 8.0), 0.14
Q3 v. 5	**7.0 (0.7, 10.1), 0.66**	**12.0 (6.1, 17.8), 0.90**	**-8.6 (-13.5, -3.7), -0.75**	-1.1 (-9.0, 4.0), -0.08
Q4 v. 5	4.9 (0.6, 9.2), 0.46	**8.5 (2.3, 14.6), 0.63**	**-7.4 (-12.4, -2.3), -0.64**	4.1 (-0.7, 9.0), 0.29
Q5 (Most)	Ref	Ref	Ref	Ref
Total Life time Adversity				
Q1 (Least) vs Q5	**8.5 (4.6, 13.6), 0.79**	**12.2 (6.1, 18.4), 0.92**	**-9.9 (-15.3, -4.5), -0.86**	**7.3 (1.2, 13.4), 0.53**
Q2 v. 5	**6.5 (2.9, 11.1), 0.61**	**12.1 (6.5, 17.6), 0.91**	**-6.7 (-11.9, -1.43), -0.58**	**5.9 (1.2, 10.7.4), 0.42**

Q3 v. 5	3.6 (-1.5, 7.3), 0.34	**10.5 (6.1, 16.1), 0.79**	**-6.0 (-10.8, -1.18), -0.52**	2.8 (-2.01, 7.58), 0.20
Q4 v. 5	2.8 (-1.3, 7.3), 0.26	4.6 (-0.8, 10.0), 0.34	**-5.5 (-10.6, -0.37), -0.48**	**4.7 (0.02, 9.3), 0.34**
Q5 (Most)	Ref	Ref	Ref	Ref

Estimates from multivariable linear regression model implemented using SAS Proc Genmod. Clustering by household of residence. Adjustment for caregiver (age, sex, employment, income dependency, perceived social standing) and child factors (age, sex, BMIZ). Multivariable models did not simultaneously adjust for different stress indicators.



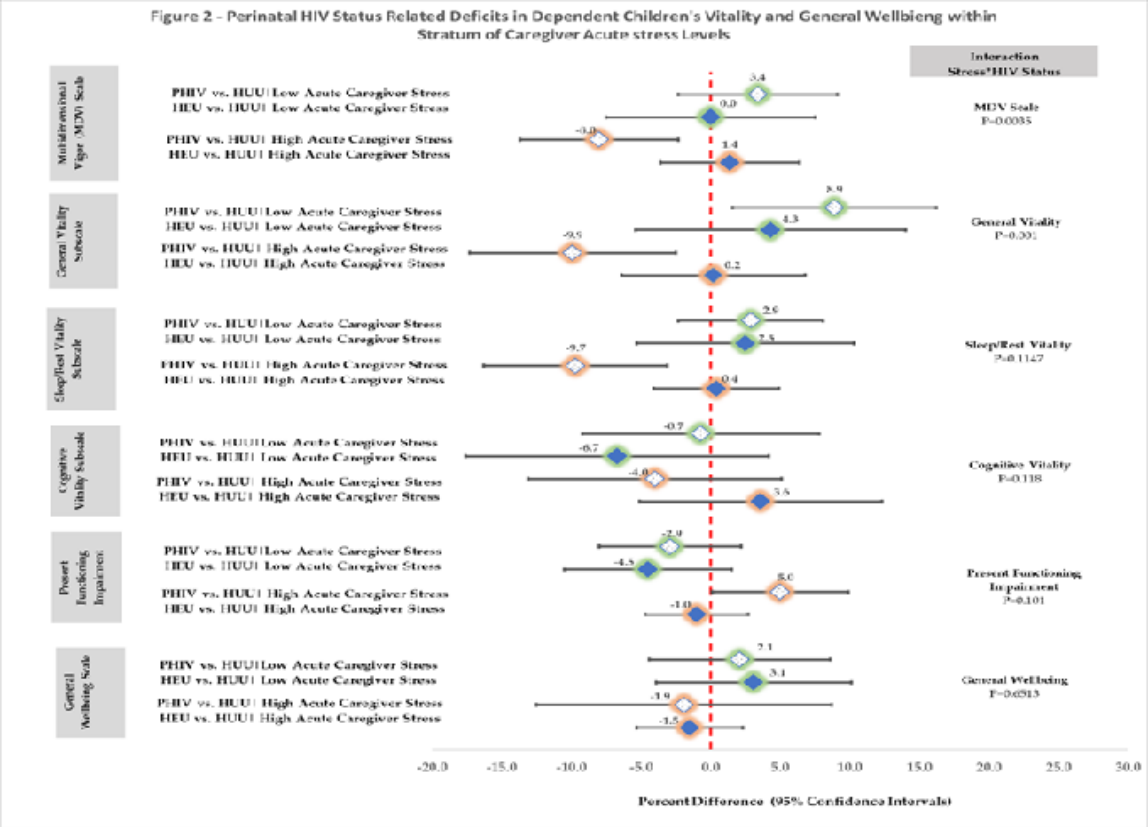


Table S1 – Further Description of Laboratory Measures by Child Perinatal HIV status

	Overall	**HUU (n=89)**	**HEU(n=92)**	**PHIV (n = 101)**	P-value
HPA-Axis Hormones					
Cortisol (nmol/L)		71.7 (64.0)	67.6 (72.6)	64.5 (76.7)	0.780
Dopamine to Creatinine ratio	2.48 (0.52)	2.47 (0.50)	2.50 (0.56)	2.46 (0.51)	0.530

Epinephrine to Creatinine ratio	0.65 (0.44)	0.62 (0.43)	0.62 (0.47)	0.69 (0.42)	0.610
Norepinephrine to Creatinine ratio	1.32 (0.35)	1.33 (0.34)	1.29 (0.37)	1.35 (0.36)	0.600
Cortisol to Creatinine ratio	1.52 (0.44)	1.50 (0.42)	1.56 (0.43)	1.51 (0.46)	0.520
Inflammation Indices	n (%)	n (%)	n (%)	n (%)	
High Eosinophils††	62 (22)	20 (23)	24 (26)	18 (18)	0.401
Neutropenia	71 (25)	15 (17)	17 (19)	39 (39)	0.001
Thrombocytosis	49 (17)	13 (15)	18 (19)	18 (18)	0.685
High CRP	47 (17)	7 (8)	15 (17)	25 (25)	0.006
White Blood Cell Count†					
Normal	176 (68)	60 (74)	58 (68)	58 (62)	0.165
High	4 (2)	0 (0)	3 (3)	1 (1)	
Low	88 (31)	23 (26)	28 (30)	37 (37)	
Lipid Profile/Metabolic Indices					
High Total Cholesterol	24(10)	7 (8)	4 (5)	13 (16)	0.092
Low HDL Cholesterol	91 (33)	31 (35)	37 (42)	23 (23)	0.043
High LDL Cholesterol	36 (13)	9 (10)	8 (9)	19 (19)	0.057
High Non-HDL Cholesterol	16 (6)	4 (5)	1 (1)	11 (13)	0.010
High Total to HDL Cholesterol Ratio	52 (18)	14 (16)	21 (23)	17 (17)	0.430
High Triglycerides	21(8)	5 (6)	4 (4)	12 (12)	0.090
Creatinine (mmol/L) mean (SD)	6.1 (13.6)	6.2 (4.2)	7.6 (22.8)	4.8 (3.0)	0.347
Serum Albumin (g/L) mean (SD)	45.3 (2.9)	45.1 (2.8)	45.0 (2.8)	45.8 (3.1)	0.090
Hematologic Status Indices					
Type of anemia					
No anemia of any kind	147 (52)	56 (63)	64 (69)	27 (27)	
Microcytic Anemia	47 (17)	22 (25)	19 (20)	6 (7)	<0.001

Macrocytic Anemia	80 (28)	8 (9)	9 (10)	63 (62)	
Anemia of Chronic Disease	9 (3)	3 (3)	1 (1)	5 (5)	
Hemoglobin (g/dL) mean (SD)	13.1 (1.3)	13.2 (1.0)	13.1 (1.5)	13.0 (1.3)	0.330
Ferritin status					
Hypo ferritinemia	25 (9)	10 (12)	6 (7)	9 (10)	0.079
Normo ferritinemia	209 (79)	69 (80)	64 (74)	76 (83)	
Hyper ferritinemia	31 (12)	7 (8)	17 (20)	7 (8)	

†: High WBC is suggestive of an active infection; Low WBC is suggestive of an auto-immune disorder or destruction of WBCs at level of the bone marrow. ††: increased values due to endemic intestinal parasitic infections such as soil transmitted helminths, schistosome infection, H. nana, etc.

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